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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/393,066	02/23/1995	JOHN H. WOLFE	PENN-0065	1030

7590 05/02/2003

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EXAMINER
CROUCH, DEBORAH

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/393,066	WOLFE ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 February 1995* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicant's arguments filed March 10, 2003 in paper no. 24 have been fully considered but they are not persuasive. The amendment has been entered. Pending claims are 1-9.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons present in the office action mailed October 11, 2002, paper 22.

Claims 1-9 are drawn to a method of stably expressing a selected DNA sequence in the central nervous system of a mammal, comprising administering to the mammal a neurotropic virus which infects cells of central nervous system of the mammal, the vector containing a selected DNA sequence operatively linked to a selected promoter so that the selected DNA sequence is stably expressed by infected central nervous system cells, to a method of stably expressing β-glucuronidase in the brain of a mammal comprising administering to the mammal a neurotropic viral vector which infects cells of the brain of the mammal, said vector being and HSV-1 vector containing a DNA sequence encoding β-glucuronidase operatively linked to a LAT promoter, so that the infected brain cells stably express β-glucuronidase.

While the claimed invention requires only stable expression of the selected DNA sequence, the specification provides no use for mere stable expression. The specification is very clear that the purpose of the delivery method to produce a gene therapy (specification,

page 2, line 3 to page 3, line 17; page 8, lines 9-13; page 9, line 34 to page 10, line 9; page 16, lines 1-17 and page 20, lines 7-10).

Applicant argues that the specification does not restrict the use of the claimed invention only to gene therapy. Applicant argues that at pages 9-10, bridg. parag., the specification discloses molecules that maybe expressed in the CNS without restricting their use to gene therapy. Applicant argues that the methods could be used to produce an animal model. Applicant argues that the methods can be used to produce an animal model of a CNS disease. These arguments are not persuasive.

A review of pages 9-10, bridg. paragraph makes reference to the method being used in somatic gene transfer suitable for a "variety of neurological disorders" and that the method can be used to administer compounds that "alter neurological function in a useful way." At both of these cites, the specification discloses very specific neurological disorders, such as MPS VII and neurological functions, such an increase in tyrosine hydroxylase in Parkinson's disease. These are clear contemplations of gene therapy. Further the administration of HSV vector encoding compounds that bind to opiate receptors to modulate drug effects also falls under the heading of gene therapy. The skilled artisan reading these passages would have interpreted that the disclosure was directed to gene therapy.

Furthermore, the specification does not disclose a use of the method in the production of an animal model. The specification is to disclose the intended use of the claimed invention at the time of filing. Applicant cannot come back post-filing to claim uses for their invention.

Applicant argues that the cited general references of Verma, Marshall, Anderson and Blau do not address the use of neurotropic viruses to deliver genes to the CNS. This argument is not persuasive.

While the above-mentioned references do not discuss neurotropic viruses, they do set the state of the general art of gene therapy at the time of filing.

Applicant argues that Fink may tech that the length of transgene expression was an unpredictable parameter of gene therapy, the use of HSV for gene therapy for gene therapy was predictable. Applicant argues that Fink teaches that replication defective HSV vectors result in little cytotoxicity and that these defective vectors can still establish latency. Applicant argues that the specification demonstrates expression from an HSV vector for four months, and that this addresses the unpredictability due to transgene expression discussed by Fink. This argument is not persuasive.

The establishment of latency does not seem to be sufficient. Fink cites Wolfe et al, using a vector such as that presently disclosed, and state that the number of cells expressing the β-glucuronidase transgene decreases dramatically with time. This statement indicates an expression insufficiency with a HSV-1-LAT vector expressing a therapeutic protein (Fink, page 288, col. 3, lines 8-14).

Applicant argues that Wolfe states that too little enzyme was present to measure β-glucuronidase activity, but adds that vector-corrected cells may have been expression near normal amounts of GUSB. Applicant argues that Verma states that that gene transfer to just a few hundred cells of the brain could considerably benefit patients with neurological disease. Applicant argues that while Wolfe states that too few cells have been corrected to alter a disease phenotype, the overcoming of the length of transgene expression from an HSV vector could provide benefit to neurological disease patients. These arguments are not persuasive.

The vector used in Wolfe are either the same or nearly the same as the HSV vector disclosed in the present specification. However long the expression of glucuronidase was in Wolfe, it wasn't sufficient to correct a disease phenotype. This clearly points to the

unpredictability of the claimed invention when viewed for its only disclosed use as a gene therapy vector.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1,2,4,5 and 6 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by US Patent5,849,572 issued December 15, 1998 (Glorioso).

Glorioso teaches the injection of an HSV-1 vector comprising a LAT promoter operatively linked to a LacZ gene into rat hippocampus (col. 8, lines 16-32). Further Glorioso teaches that expression of LacZ was detected 10 months after injection into the hippocampal region of the rat brain, indicating stable expression (col. 8, line 32-35). Glorioso teaches that for Parkinsonian gene therapy evaluation, an HSV-1 vector comprising the LAT promoter operatively linked to a tyrosine hydroxylase gene can be injected into rat hippocampus (col. 6, lines 60 to col. 7, line 11). Thus, Glorioso clearly anticipates the claimed invention.

Applicant argues that the claims have been amended to state that expression is at least for four months. However, the newly cited art, Glorioso, teaches expression for six months. Thus, Glorioso anticipates the claimed invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 7 are rejected under 35 U.S.C. § 103 as being unpatentable over US Patent 5,849,572 issued December 15, 1998 (Glorioso) in view of Dobson et al (1989) J. Virol. 63, 3844-3851.

Glorioso teaches the injection of an HSV-1 vector comprising a LAT promoter operatively linked to a LacZ gene into rat hippocampus (col. 8, lines 16-32). Further Glorioso teaches that expression of LacZ was detected 10 months after injection into the hippocampal region of the rat brain, indicating stable expression (col. 8, line 32-35). Glorioso does not teach the specific HSV strain used to produce the HSV-1-LAT vector. Dobson teaches that three HSV-1 strains have been sequenced in the latency region, and that they have the same structure, one of which is HSV-1 strain 17syn+ (page 3844, col. 1, parag. 2). At the time of filing, it would have been obvious to the ordinary artisan to produce and stably expression in the CNS, the HSV-1-LAT vector disclosed in Glorioso using HSV-1 strain 17 as HSV-1 strain 17 because of equivalent genomic structure between HSV-1 strains as taught by Dobson. Thus for stable expression of a selected DNA sequence in the CNS, Glorioso in view of Dobson offers sufficient teachings and motivation for the ordinary artisan to make and use the claimed invention at the time of filing.

Claims 1, 3, 8 and 9 are rejected under 35 U.S.C. § 103 as being unpatentable over US Patent 5,849,572 issued December 15, 1998 (Glorioso) in view of Dobson et al (1989) J. Virol. 63, 3844-3851 and Guise et al (1985) Gene 34, 105-110.

Glorioso teaches the injection of an HSV-1 vector comprising a LAT promoter operatively linked to a LacZ gene into rat hippocampus (col. 8, lines 16-32). Further Glorioso teaches that expression of LacZ was detected 10 months after injection into the hippocampal region of the rat brain, indicating stable expression (col. 8, line 32-35).

However, Glorioso does not disclose the HSV-1 strain used to produce the HSV-1 vector nor the expression of β-glucuronidase. Dobson also teaches that three HSV-1 strains have been sequenced in the latency region, and that they have the same structure, one of which is HSV-1 strain 17syn+ (page 3844, col. 1, parag. 2). Guise teaches a cDNA clone encoding human β-glucuronidase (page 108, col. 1-2, bridg. parag.). Guise further teaches that defects in the gene encoding β-glucuronidase cause a human disease, mucopolysaccharidosis VII (page 105, col. 1 and 2).

Thus, at the time of the instant invention, it would have been obvious to the ordinary artisan to provide stable expression of β-glucuronidase in the CNS comprising administering an HSV-1 vector comprising the LAT promoter operably linked to a DNA sequence encoding β-glucuronidase. Likewise, it would have been obvious to the ordinary artisan to produce and stably expression in the CNS, the HSV-1-LAT vector disclosed in Glorioso using HSV-1 strain 17 as HSV-1 strain 17 because of equivalent genomic structure between HSV-1 strains as taught by Dobson. Motivation for administering the HSV-1 vector comprising a LAT promoter operably linked to a DNA sequence encoding β-glucuronidase comes from Glorioso teaching that HSV-1 can be used in gene therapy, that HSV-1-LAT forms stable expression, and that administering HSV-1-LAT construct as a preliminary study prior to gene therapy (col. 6, lines 60 to col. 7, line 11). Guise offers motivation in stating that inactive β-glucuronidase is responsible for a glycogen storage disease. Thus, for stably expression of β-glucuronidase in the CNS, the cited prior art provides sufficient teachings, suggestion and motivation.

Applicant argues that Palella does not teach four months of expression as now claimed. In response, the examiner points to the newly cited reference, Glorioso, which teaches expression for six months.

Applicant also argues that Palella, Dobson and Nishimura do not shown CNS expression. In response, the examiner notes that newly cited reference, Glorioso, does teach CNS expression.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 703-308-1126. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

dc
April 30, 2003